UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,379	01/25/2002	Tasuku Honjo	Q61531	7110

23373 7590 02/20/2004

SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,379	HONJO ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *11-13* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendment filed 18 December 2003 has been received and entered in full. Claims 1-10 and 14-15 have been cancelled. Claims 11-13 have been amended.

2. All Objections and Rejections not herein maintained are *withdrawn.*

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

4. The Objection to the Specification as set forth at ¶6-7 pp. 3 in the previous Office Action (18 August 2003) is hereby *withdrawn* in view of Applicant's amendments (18 December 2003).

5. The Rejection of claims 1-8 and 10-13 under provisional obvious-type non-statutory double patenting as set forth at ¶8-11 pp. 3-4 in the previous Office Action (18 August 2003) is *moot* in view of the abandonment of Applications Nos. 09/083,002 and 10/041,016.

6. The Rejection of claims 1-8 under 35 U.S.C. §112 ¶1 as set forth at ¶12-20 pp. 4-9 in the previous Office Action (18 August 2003) is *moot* in view Applicant's cancellation of said claims (18 December 2003).

7. The Rejection of claim 10 under 35 U.S.C. §112 ¶1 as set forth at ¶21-30 pp. 9-12 in the previous Office Action (18 August 2003) is *moot* in view Applicant's cancellation of said claim (18 December 2003).

8. The Rejection of claims 11 and 12 under 35 U.S.C. §112 ¶1 as set forth at ¶21-30 pp. 9-12 in the previous Office Action (18 August 2003) is *moot* in view Applicant's amendment of said claims from a product to a method (18 December 2003). The Examiner notes that the amendment has been entered and requires a new rejection to address the change from a product to a method and is included herein.

9. The Rejection of claim 13 under 35 U.S.C. §112 ¶1 as set forth at ¶31-39 pp. 12-15 in the previous Office Action (18 August 2003) is *withdrawn* in view Applicant's amendment (18 December 2003). The Examiner notes that the amendment has been entered and requires a new rejection to address the new limitations and is included herein.

10. The Rejection of claims 4 and 5 under 35 U.S.C. §112 ¶2 as set forth at ¶40-41 pp. 15 in the previous Office Action (18 August 2003) is *moot* in view Applicant's cancellation of said claims (18 December 2003).

11. The Rejection of claims 1-8 and 10 under 35 U.S.C. §102(e) as set forth at ¶43 pp. 16-17 in the previous Office Action (18 August 2003) is *moot* in view Applicant's cancellation of said claims (18 December 2003).

12. The Rejection of claims 11 and 12 under 35 U.S.C. §102(e) as set forth at ¶43 pp. 16-17 in the previous Office Action (18 August 2003) is *moot* in view Applicant's amendment of said claims from a product to a method (18 December 2003). The Examiner notes that the amendment has been entered and requires a new rejection to address the change from a product to a method and is included herein.

13. The Rejection of claim 13 under 35 U.S.C. §102(e) as set forth at ¶43 pp. 16-17 in the previous Office Action (18 August 2003) is *withdrawn* in view Applicant's

amendment (18 December 2003). The Examiner notes that the amendment has been entered and requires a new rejection to address the new limitations and is included herein.

Claim Rejections - 35 USC § 112

14. Claims **11** and **12** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

15. Applicant traverses the rejection of the product claims in the previous Office Action (18 August 2003) on the following grounds: **(a)** Examples 8 & 10, Figures 1 & 2 demonstrate that the SEQ ID NO: 13 and 14 are effective to inhibit proliferation of cultures smooth muscle muscles, even after treating these cells with a mitogen (PDGF) therefore the Specification is enabled for the therapies claimed.

16. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

17. On "**(a)**", Examples 8 & 10 as well as Figures 1 & 2 teach exactly what applicant has stated. SEQ ID NO: 13 and SEQ ID NO: 14 are effective to inhibit proliferation of cultures smooth muscle muscles, even after treating these cells with a mitogen (PDGF). This however does not adequately support the full breath of the claims as discussed below.

18. The claims are drawn very broadly to methods of treatment for abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis (narrowing at the site of balloon

dilatation in a vessel) after PTCA ("percutaneous transluminal coronary angioplasty"), and/or myosarcoma comprising administering SEQ ID NO: 13 or 14, or sequence derivatives thereof, or fragments thereof which inhibit smooth muscle cell proliferation. The language of said claims encompasses a wide range of diseases. The Examiner notes that atherosclerosis is the most common form of arteriosclerosis.

19. The specification teaches that SEQ ID NO: 11, 12, and 15 encode SEQ ID NO: 13 and 14. A preparation comprising SEQ ID NO: 14 has activity as an inhibitor of aortic vascular smooth muscle proliferation *in vitro* (Figure 2).

20. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed signs, symptoms, or indicators of an alleviation of abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, and/or myosarcoma in a patient methods of using SEQ ID NO: 13 or 14 or sequence derivatives thereof, or fragments thereof which inhibit smooth muscle cell proliferation as a therapeutic agent.

21. The specification fails to provide any guidance for the successful treatment of abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, and/or myosarcoma using SEQ ID NO: 13 or 14 or sequence derivatives thereof, or fragments thereof which inhibit smooth muscle cell proliferation. Further the resolution of the various complications in regards to targeting the role a particular protein in abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, and/or myosarcoma is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below,

the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known related proteins to practice a therapy abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, and/or myosarcoma. In addition, the skilled artisan must identify which signs and symptoms of abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, and/or myosarcoma to correlate with an alleviation of symptoms resulting from practicing the invention as claimed. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

22. Additionally, a person skilled in the art would recognize that predicting the efficacy of using SEQ ID NO: 13 or 14 or sequence derivatives thereof, or fragments thereof which inhibit smooth muscle cell proliferation *in vivo* based solely on its performance *in vitro* is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* therapies, such a disclosure would not be considered enabling since the state of protein biochemistry and therapies for abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, and/or myosarcoma are highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

23. The following references are cited herein to illustrate the state of the art of protein biochemistry and the disease states in the claims.

24. On the nature of the invention, Nakamura *et al.* (6 August 1999) "DANCE, a Novel Secreted RGD Protein Expressed in Developing, Atherosclerotic, and Balloon-injured Arteries." The Journal of Biological Chemistry **274**(32): 22476-22483 teaches a polypeptide that shares 100% sequence homology with SEQ ID NO: 13 and 14 (Figure 1). The novel polypeptide discussed by Nakamura et al. is called DANCE: developmental arteries and neural crest epidermal growth factor (EGF)-like and it is shown to mediate adhesion of endothelial cells through binding to integrins *in vitro* (Figure 10). Thus while establishing a function for the claimed proteins, the reference does not teach what fragments, homologues, or fragments of homologues retain DANCE activity or what the therapeutic effects of DANCE would be as there are not examples provided in the instant specification.

25. Further on the nature of the invention, Ross (14 January 1999) "Atherosclerosis—An Inflammatory Disease." The New England Journal of Medicine **340**(2): 115-126 atherosclerosis, the most common form of arteriosclerosis, is a complex process that begins with the appearance of cholesterol-laden macrophages (foam cells) in the intima of an artery. Smooth muscle cells respond to the presence of lipid by proliferating, under the influence of platelet factors. Therefore it is a complex disease with multiple intertwined steps, none of which are linked in any way to SEQ ID NO: 13 or 14 or sequence variants or fragments thereof.

26. On the level of predictability in the art, Biegelsen & Loscalzo (June 1999) "Endothelial function and arteriosclerosis." Coronary Artery Disease **10**(4): 241-256 teaches that the vascular endothelium exerts vasodilator, antithrombotic, and growth-inhibiting effects on the vessel wall. In arteriosclerosis, the vascular endothelium is dysfunctional, contributing to vasoconstriction, thrombosis, and growth of vascular smooth muscle (pp. 241). Therefore it is not clear from the claims or the Specification as to the therapeutic activity that would be produced by SEQ ID NO: 13 or 14 or sequence variants or fragments thereof. The skilled artisan is not apprised of which mechanism or pathological effect is assuaged or otherwise mitigated by treatment with SEQ ID NO: 13 or 14 or sequence variants or fragments thereof in view of the multiple factors at play in arteriosclerosis.

27. On the amount of direction provided by the Inventor (in the Specification), no nexus between arteriosclerosis, restenosis after PTCA, or myosarcoma. For instance, Mentzel *et al.* (October 1998) "Low-grade myofibroblastic sarcoma: analysis of 18 cases in the spectrum of myofibroblastic tumors." The American Journal of Surgical Pathology **22**(10): 1228-1238 teaches that myosarcomas (or tumors originating from myoblast derived cells such as smooth muscle) cover a wide range of tumors with different anatomical origins, histochemical profiles, sizes, and patient ages (Table 1 and 2). Thereof the skilled artisan is not apprised of which rate determining step or critical pathological element which SEQ ID NO: 13 or 14 or sequence variants or fragments thereof address for treatment.

28. On the amount of experimentation necessary to practice the invention based on the Specification as filed, as noted above, no nexus between any of the diseases listed in

the claims and SEQ ID NO: 13 or 14 or sequence variants or fragments thereof has been established in the claims or shown in the art. Therefore the skilled artisan is left to explore arteriosclerosis, restenosis after PTCA, and myosarcoma to first identify a link between said conditions and any one of SEQ ID NO: 13 or 14 or sequence variants or fragments thereof. Next, the skilled artisan must identify a rate-determining-step or critical pathological element of said conditions that SEQ ID NO: 13 or 14 or sequence variants or fragments thereof are involved in or interact with to a significant degree. Finally the skilled artisan must evaluate the effects of administering SEQ ID NO: 13 or 14 or sequence variants or fragments thereof to a patient or animal model with arteriosclerosis, restenosis after PTCA, and myosarcoma. For instance, Ferns & Avades (April 2000) "The Mechanisms of coronary restenosis: insights from experimental models." International Journal of Experimental Pathology **81**(2): 63-88 teaches that several cellular and molecular events occur following a balloon angioplasty. Soon after the balloon dilation, the arterial site becomes inflamed leading to leukocyte infiltration and platelet activation (pp. 64). This is followed by reorganization of the smooth muscle cells including apoptosis and extracellular matrix restructuring (pp. 65-66; Figure 1). In a successful treatment, both the inflammation and smooth muscle phenotype changes occur without damage and the vessel heals. However in restensosis the complex series of steps including but not limited to the coordinated proliferation of medial smooth muscle cells, the migration of a subpopulation of medial smooth muscle cells, the proliferation of intimal smooth muscle cells, and the elaboration of extracellular matrix (changing architecture), and vascular remodeling goes astray (pp. 66). This leads to the narrowing of the arteries and the complications which followed. However, the skilled artisan is not

presented with which, if any, of the steps of this complicated condition are acted upon by SEQ ID NO: 13 or 14 or sequence variants or fragments thereof thus presenting an invitation to experiment [see also Kagan & Myers (June 1998) "Mediators of restenosis." Surgical Clinics of North America **78**(3): 481-500].

29. Regarding sequence derivatives and fragments of SEQ ID NO: 13 and 14 polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the

invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

30. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of abnormal growth of a smooth muscle cell, arteriosclerosis, restenosis after PTCA, or myosarcoma as exemplified in the references herein.

31. Claims **11-13** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

32. Applicant traverses the rejection of the product claims in the previous Office Action (18 August 2003) on the following grounds: **(a)** Examples 8 & 10, Figures 1 & 2 demonstrate that the SEQ ID NO: 13 and 14 are effective to inhibit proliferation of cultures smooth muscle muscles, even after treating these cells with a mitogen (PDGF) and any such homologues, sequence variants, and fragments must have this activity to satisfy the claim requirements.

33. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

34. On "**(a)**", Examples 8 & 10 as well as Figures 1 & 2 teach exactly what applicant has stated. SEQ ID NO: 13 and SEQ ID NO: 14 are effective to inhibit proliferation of cultures smooth muscle muscles, even after treating these cells with a mitogen (PDGF). This however does not adequately support the full breath of the claims as discussed below.

35. The claims are drawn to methods reciting polypeptides having at least 90% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

36. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 13 and 14. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

37. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

38. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

39. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 13 and 14, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

40. Claim **13** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons as set forth at ¶42 pp. 15 in the previous Office Action (18 August 2003).

41. The Examiner respectfully suggests amending the claims to distinguish between antagonist and agonist as a way to *obviate* this rejection.

42. Claim **13** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

43. The term "modulate" in claim 13 is a relative term which renders the claim indefinite. The term "modulate" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. "Modulate" is given a broad, poorly defined definition in the art and the Specification. It may pertain to inhibitors, activators, agonists, antagonists, etc. It is not clear which class of compounds the invention identifies.

Summary

44. No claims are allowed.

45. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

46. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
February 17, 2004